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STUDIES ON DIPHTHERIA IN CLEVELAND, I*

DIPHTHERIA-CARRIERS

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INTRODUCTION

This paper forms the beginning of a series of studies of diphtheria in Cleveland with special reference to the problem of shortening the average quarantine period as far as is consonant with the safety of the public. The material available is perhaps of unusual character, inasmuch as it represents the combined material of the division of health, the contagious department of the City hospital, and the various infant asylums and other similar institutions in and about Cleveland. Through the co-operation of the municipal authorities, the Western Reserve medical school, and certain of the private institutions, it has been possible to gain access wherever desired, and the development of these opportunities gives promise of an even more abundant material in the future.

The matter is being taken up from a variety of standpoints, among which the morphologic and immunologic are prominent in the present series. From year to year the statistics of diphtheria in Cleveland are being worked out under the direction of one of us by students in the medical school of Western Reserve University, as theses for the course in hygiene, and published in the Cleveland Medical Journal. When the number of cases recorded and analyzed is sufficient, the statistical side will be considered.

We desire to thank the division of health for assistance in the use of the records, and the various institutions for the courtesy with which they have met our desires and suggestions.

THE INCIDENCE OF DIPHTHERIA-CARRIERS IN CLEVELAND

The problem of diphtheria-carriers is one of the most important in the management of this disease, for it is probable that the spread and continuance of the epidemics are due largely to the presence of diph-

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theria bacilli in the throats of apparently healthy persons. The literature at present is so filled with articles on the number of such persons and on the results of various attempts to get rid of the organisms that one hesitates to add further articles to the array. The fact, however, that we have been able to combine in Cleveland a number of series of cultures from a variety of sources with some degree of careful investigation into the various groups seems to offer justification for such an addition.

Definition of Carrier.—In order that our investigations and our results may be clearly interpreted, certain facts must be set down. The first of these has to do with the question: What is a diphtheria-carrier? A diphtheria-carrier is a person free from clinical symptoms of diphtheria, who carries virulent B. diphtheriae in the nose or throat for a period of more than 21 days.

The significant word in this definition is "virulent," and the question of virulence is our chief stumbling block. We note in our series that there are: (1) organisms morphologically and culturally B. diphtheriae, but incapable of producing diphtheria toxin, occurring in all groups; and (2) organisms of a similar morphologic type, occurring in large numbers in institutions where detailed cultural investigations are not practicable. In these institutions there has been no epidemic of diphtheria, and indeed no cases have come under treatment for a period of years, these facts suggesting that the virulence must be comparatively low.

Moreover, we feel that tho inoculation of guinea-pigs with fatal results and recovery of the organism is diagnostic of virulence, yet it does not follow that organisms failing to cause the death of guinea-pigs are nonvirulent for man, tho the probability of this is strong.

In general, then, an organism isolated from nose or throat, and morphologically identical with known virulent types, may be virulent or avirulent. Establishment of cultural reactions identical with those of the virulent type still offers no further proof. Only where animal inoculations are possible can the determination of virulence be made. The recent work of Zingher and his co-workers[2] simplifies this to a large extent but still leaves the condition of the poorly financed laboratory unsatisfactory, so that while some cases may be released while still dangerous, more will be quarantined beyond the necessary period.

In addition to virulence, we must establish the date after diagnosis on which the carrier state may be said to begin. This must of necessity be arbitrary, as no two cases become free after exactly the same interval. In the tabulation of our results we found that the average duration of quarantine, estimated from the records of the bureau of laboratories for 1913, 1914, and 1915, was 20.5 days, so that an arbitrary basis of 21 days was established. This calculation is based of course on those cases only in which a diagnosis of diphtheria had been made, and in which therefore we may infer the persistence, after convalescence, of a virulent organism. It gives us no information as to the carriers with no history of infection, in whom the presence of the organisms is established accidentally. The Schick test is helpful in that it has been established that all carriers must be negative to this test; but of course at present only a very small percentage of any community has been tested.

On the basis of the evidence available in Cleveland to the present time, we must consider as carriers all in whom morphologic B. diphtheriae persists beyond 21 days.

Analysis of Cleveland Series.—Various attempts to ascertain the average number of diphtheria-carriers in a given population have shown a surprisingly large number, and one of the purposes leading to the preparation of this paper was to establish a similar average for Cleveland. To the routine cases coming to the laboratory for diagnosis, we have added certain groups of persons who were examined with the sole view of establishing the presence or absence of B. diphtheriae or of other types. As will be noted in the detailed morphologic investigation, we have taken certain standards as representing certain types, and it is on these standards that our figures are based. The investigation covered the following groups:

A. Public Schools.—Of 1,024 children in grade schools scattered over the city, ranging in age from 9 to 12 years (the children of a given grade in each school being examined on the same day), 42, or 4.2%, showed morphologic B. diphtheriae.

B. Orphan Asylum.—This group is of special interest inasmuch as for 6 years there has been no diphtheria reported from the institution, nor has any antitoxin been given. The cultures were originally taken in the hope of establishing more data as to the throat flora under such conditions, but the results in this connection must be taken cautiously, as the children have free intercourse with the street children of a crowded district. Moreover, several cases of tonsillitis and sore throat have been treated each year. The records of the hospital ward, however, show no serious cases of illness in any way attributable to diphtheria, nor have there been any after effects suggestive of diphtheria paralysis. This would indicate that, if any of the cases of tonsillitis were diphtheria, they must have been mild. Moreover, in such cases as were tested on animals no virulence was found.

Of 429 children in this asylum, in ages ranging from 4 to 15, with separate cultures from nose and throat in each case, or 858 cultures in all, 46 showed morphologic B. diphtheriae in the throat alone, 2 in the nose alone, and 2 in both. This gives 11.2% carrying morphologic B. diphtheriae.

In connection with an epidemic of cerebrospinal meningitis a year later, cultures were made from all the inmates of this same asylum. In 11 of 535 persons morphologic B. diphtheriae was found, the results showing just over 2% carriers as against 11% one year previously.

C. Babies' Dispensary.—Of 558 routine cases coming to the Babies' dispensary, 3 showed morphologic B. diphtheriae, and the cultures in these cases were fatal for guinea-pigs. The patients in this series being all under 3 years of age, the contact with other children was more limited than in the other groups. The percentage of 0.54 showing morphologic B. diphtheriae was markedly lower than that of other groups, but all found were virulent.

D. Boys' Reform School.—Here, among boys from 6 to 18, two sets of cultures were made at a 5 or 6 weeks' interval in relation to an outbreak of diphtheria. The farm is in the country some miles from Cleveland, so that contacts can be accurately determined. The apparent etiology of the epidemic was a new boy who ran away after 48 hours' detention and later turned up in Cleveland with a clinical case of diphtheria, from which at least one contact case developed, showing the virulence of the organism. Three days after his departure from the farm the first case developed there. The culture was sent in to the laboratory of the division of health, and some of the staff were detailed to make cultures and Schick tests on all inmates, except those suffering from clinical diphtheria. Of the cultures from 175 boys, there were 7 in the first set and 8 in the later set, or 4% and 4.5%, that yielded morphologic B. diphtheriae.

All the boys who gave positive Schick tests were given antitoxin and no further cases developed.

E. Infants' Asylum.—Of 53 cultures from children ranging in age up to 5 years, none showed morphologic B. diphtheriae. Our record of a second trial at this asylum is omitted, as the interval was only a few weeks, and the results identical with those of the first.

This gives a total of 2,774 persons examined in special investigations in and about Cleveland, among whom we obtained 105 cultures of morphologic B. diphtheriae, a percentage of 4.07. The results of Moss[6] in Baltimore showed a percentage of 3.5.

Routine Diagnosis Series.—The cases sent to the city laboratory for diagnosis were clinically sore throat, and were interesting from the carrier standpoint in regard to the length of quarantine, giving an index of the time during which convalescence may be dangerous.

Period of Quarantine.—During the last 3 years careful records have been made of the length of quarantine in these cases. In 1913 there were 2,067 houses quarantined, in 1914 there were 1,795 houses and during the first 10 months of 1915 there were 981 houses. This excludes all from which the patients were transferred to the city hospital prior to the last part of 1914, as their cultures up to that time did not come to us for release, and excludes also all in which cases terminated fatally. A small error must be considered here inasmuch as the length of the quarantine period was taken as the length of the quarantine of the house, so that when several cases followed one another in the same family, the quarantine was not raised until the last case showed 2 negative tests. The proportion of such cases, however, was small, and the labor of following out the individual details would have been excessive.

TABLE 1

PERIOD OF QUARANTINE

Days	1913	1914	1915 (10 mo.)
3 to 10	404	125	118
10 to 20	731	968	490
20 to 30	401	426	240
30 to 40	240	146	87
40 to 50	124	48	26
50 to 60	61	14	13
60 to 70	35	8	6
70 to 80	27	4	1
80 to 90	23	3	...
Over 90	21	3	...
Total quarantine	2067	1745	981
Average number of days	22.9	19.7	18.9

Total houses quarantined 4843; average quarantine for the 3 years 20.5 days.

The table is inserted here in the same form as for the annual reports of the health division. The summarization shows that over one-half the quarantines terminated before the end of the 3rd week, but that in a comparatively small number of cases organisms persisted for a period measured in months.

MORPHOLOGIC STUDIES

Much time has been spent on this phase of the question, but the difficulties entailed in the study of an organism with such a tendency to mutation are so great, and the use of terms in current literature is so confusing, that investigations have been undertaken from a different point of view, which will be presented in a subsequent paper. On account of this notable confusion in the literature, it appears necessary to establish clearly our own definitions, so that when we speak of diphtheria, pseudodiphtheria, and so forth, our meaning, at least, may be clear.

Terminology.—The use of the words "type" and "form" as interchangeable terms appears to us unjustifiable. A type must remain constant, and may be the precursor or the basis of a variety of forms. In our experience a culture containing only one type is very rare, if indeed it exists, and careful examination will usually show several types under the Wesbrook classification. With possibly rare exceptions, we consider B. diphtheriae in 15- to 24-hour cultures as an organism of rod form staining irregularly and containing metachromatic granules. Our commonest form shows two lightly staining areas adjacent to the granules, leaving a cleft in the center. Marked variations occur with alterations in the source, in the reaction and moisture of the culture medium, and even in the method of its sterilization. That a change in the chemical or biologic conditions of the throat may also cause variations is suggested by the fact that the diagnostician can often diagnose a culture as "for release" by morphology alone.

Diphtheria-like Organisms.—Most prominent is the Hofman-Wellenhof organism. As to the virulence of different forms of diphtheria bacilli, it is surprising, after the large amount of investigation, to note the great variance of opinions even at the present day, a matter of some importance when one laboratory contradicts the opinion of another as to a diagnosis culture. In view of the work in hand and of the large number of articles on the subject already in print, we shall not attempt here to analyze the opinions on this point, further than to summarize.

Some authors hold that the Hofman or D_2 type is at times pathogenic, and have claimed mutation between this type and the typical one in both directions; others believe that the phenomenon of virulence or avirulence is a permanent one; others report virulent pseudodiphtheria not affected by diphtheria antitoxin. In this laboratory, while we hold sub judice the statements about virulent organisms of this type, we feel that until these organisms are proved contagious in the sense that the Klebs-Loeffler bacillus is contagious, we may safely consider them as negative, and refuse to quarantine patients on their evidence. In our own experience organisms of this type have never proved virulent.

TABLE 2

MORPHOLOGY AND VIRULENCE

Source	Number of Cases	Morphologic B. Diphtheriae	Virulence	Diphtheria-like Bacilli, inc. Hofman
A. Babies' dispensary	558	3	3	175
B. Boys' reform school	175	8	..	82
C. Orphan asylum, 1914	429	46	*	132
D. Orphan asylum, 1915	535	11	..	173
E. Public schools	1024	42	..	106
E. Infants' asylum	53	0	..	23
F. Routine diagnoses	....	..	..	...
Total	2774	110	3	691

* 18 tested; none virulent.

In the interpretation of Table 2, certain points are conspicuous:

1. The large percentage of diphtheria-like organisms, more especially with respect to babies and children (A and E)—32%. Fourteen cultures were selected for further investigation; all proved nonvirulent, and nonproductive of acid in dextrose, dextrin, and saccharose. One even gave an alkaline reaction in the sugars.

2. The large percentage in the orphan asylum—37% in 1914 and 32% in 1915. In this institution, as noted elsewhere, there has been no clinical diphtheria for 6 years. Eighteen of the diphtheria-like organisms were nonvirulent and nonproductive of acid in dextrose and dextrin.

For our present purposes we have accordingly divided the organisms into 3 groups, while appreciating that the variations already noted as due to environmental factors may have led us astray at times: (1) virulent B. diphtheriae, (2) avirulent B. diphtheriae, (3) diphtheria-like organisms, including diphtheroids.

Group 1 includes irregularly staining organisms with terminal granules (including both C and D types and involution forms such as A and B). There is a tendency to parallelism. These organisms produce acid in dextrose and dextrin, but not in saccharose, and in 48-hour broth cultures are fatal to guinea-pigs in doses of 0.5% of body weight. Organisms less than 12 hours old show the usual solid forms similar to the Hofman bacillus.

Group 2 includes forms morphologically and culturally identical with those of Group 1, but not productive of toxin.

Group 3 includes several subgroups. The chief forms are those similar to Wesbrook's D_2, E_2, and G_2 with lanceolate or rounded ends, varying markedly in length. These include the Hofmann bacilli. In older cultures they may become so short as to resemble diplococci, but occasionally aging produces long forms similar to some of the involution forms of Groups 1 and 2. At from 36 to 48 hours terminal granules often develop, clouding the picture still more. Parallelism is even more marked than in Groups 1 and 2, but no acid is produced in dextrose and dextrin. In our experience these organisms are never virulent. Another subgroup is represented by B. xerosis. This is a short solid-staining form in the early cultures, becoming barred and even granular on further incubation. It never produces gas in dextrose and dextrin, but may in saccharose. It does not produce toxin. Finally, there are the so-called "diphtheroids," found in a variety of pathologic conditions, and of disputed virulence. They are readily distinguishable from diphtheria bacilli, and in addition are rarely found in the throat. There is another group of rod forms with metachromatic granules, often found in the throat and occasionally mistaken for diphtheria bacilli. These are of B. lactimorbi type, and, by the experienced worker, are easily differentiated by their more regular morphology. They form spores and are motile.

In view of our present knowledge we believe that the most satisfactory attitude in regard to diphtheria, is that which eliminates all diphtheria-like forms as etiologic factors in the disease. In methods and principles of diagnosis, there should be a greater uniformity, so that the results of one laboratory can be properly interpreted at another.

IMMUNOLOGIC STUDIES—THE SCHICK TEST

As an aid in the study of diphtheria-carriers, we decided in the early part of 1914 to make use of the so-called Schick, or intradermal, test for antitoxin in the blood. Through the kindness of Dr. W. H. Park, of the New York city research laboratories, arrangements were made enabling us to get a fresh supply of diphtheria toxin every 2 weeks.

In the beginning of the work it was deemed necessary to confirm the data as to percentages of positive and negative reactions at various ages, to determine the possibility of error in making the test and reading the reactions, and to determine the action of the test in the study of carriers.

The material was obtained from the following sources:

A. Boys' farm	175
B. City hospital. Selected cases	240
C. City hospital. Routine cases	232
D. Infant asylum	53
E. Laboratory staff (Repeated tests showed same results as original)	20
F. Medical students	38
G. Dental students	30
H. Miscellaneous	38
	826

In articles by Schick,[1] Park, Zingher, and Serota,[2] and later articles by Kolmer and Moshage,[3] and Bundesen,[4] the percentages of positive reactions found at different ages have been given. To these we add our own, which we find are quite in agreement with their findings (Table 3). With slight differences it will be seen that about 80% of infants under 1 year, from 50 to 60% of children over 10 years, and about 70% of adults have enough antitoxin in their blood to render them insusceptible to diphtheritic infection and to make unnecessary the prophylactic administration of diphtheria antitoxin if they have been exposed to the disease. Schick[5] has recently touched on this phase of the subject.

The technic for making the test has been repeatedly described, but we wish to emphasize that altho it is very easy to perform, slight errors may cause false reactions which are not easily differentiated from true reactions. The false reactions fall into several groups:

1. Those resulting from a larger amount of fluid than necessary. We agree with Kolmer and Moshage that the smaller amounts, from 0.05 to 0.1 c.c., are much better. The injection of 0.2 c.c. not infrequently gives rise to a traumatic reaction which might confuse the inexperienced person.

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[1] München. med. Wchnschr., 1913, 60, p. 2608.

[2] Arch. Pediat., 1914, 31, p. 481.

[3] Am. Jour. Dis. Child., 1915, 9, p. 189.

[4] Jour. Am. Med. Assn., 1915, 64, p. 1203.

[5] Ztschr. f. d. ges. exper. Med., 1914, 2, p. 83.

2. Those resulting from trauma due to using a large needle. We have found most satisfactory the platino-iridium No. 25. If the needle is introduced with the lumen directed upward, the white blister-like swelling will be obtained at every trial. We have never observed a false reaction from trauma persist for over 24 hours.

3. Those resulting from anaphylaxis of a general protein character. These reactions are rare, and when occurring rarely persist beyond 24 hours. Therefore by reading the reaction at the end of 48 hours most of them are eliminated.

4. Those resulting from the preservative added to the toxin solution injected. Kolmer and Moshage have noted this reaction in 46% of scarlet fever patients when 0.5 c.c. of sterile salt solution containing 0.25% of tricresol was injected intradermally.

We have found that the use of freshly sterilized salt solution gives a considerably lower number of false reactions than when old salt solution is used. The reactions obtained with old, while not as marked as the other-mentioned false reactions, still might confuse inexperienced persons.

TABLE 3

PERCENTAGES OF PERSONS SUSCEPTIBLE TO DIPHTHERIA ACCORDING TO AGE

Age in Years	Schick	Park	Kolmer	Bundesen	Perkins, Miller, Ruh	Average of Reports
Under 1	7	40.0	12.0	24.5	15.2	19.7
1 to 5	53	65.9	54.5	51.5	58.1	56.6
5 to 10	50	42.5	57.8	36.7	51.6	47.7
10 to 15	50	26.0	24.0	42.2	34.4	35.3
Over 15	10	33.0	35.0	33.0	31.0	28.4

An additional carefully checked series of 41 medical students and 28 dental students gave a surprisingly high percentage of positives, practically identical in both groups. There were in all 48 positive tests, 4 of which did not develop until the afternoon of the second day, and none of which failed to persist more than 4 days, and 21 negatives in which no reaction took place. This gives 69% of persons susceptible. Further tests, which will involve the entire personnel of the medical school, are now in progress to determine whether this high percentage was accidental or characteristic of the group.

Concerning the practical use to which the test can be put in the study of diphtheria-carriers, we believe that it offers help in making the diagnosis of a true carrier. Guthrie, Moss, and Akers,[6] in a study of the incidence of diphtheria-carriers, including over 6,000 adults, found a striking discrepancy between the number of carriers and the incidence of clinical diphtheria. In their study they find that 80 to 90% of the organisms isolated were avirulent. In our own studies similar results were obtained for those organisms tested as to virulence. Thus, in these cases in which an organism morphologically a diphtheria bacillus was found, the person would necessarily be placed in quarantine. If an intradermal test gave a positive result, the patient could be discharged without further investigation of virulence. If, however, a negative reaction was obtained, a virulence test would have to be made.

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[6] Bull. Johns Hopkins Hosp., 1915, 26, p. 88.

In our series of cases 16 carriers, according to our definition, have been subjected to Schick tests and no positive reaction has been found. This confirms the well-known fact that true carriers invariably have an antitoxin content of over 1/30 unit per cubic centimeter of blood.

In the epidemic at the Boys' farm elsewhere described, Schick tests made in the case of 175 inmates, gave positive results in 16, and a prophylactic dose of antitoxin was given each of these. No isolations were carried out other than those of the clinical cases and there were no additional infections. In a large infant asylum, of 53 children tested, 6 were positive, all of which were treated by Behring's method for active immunization. Altho only 3 became negative to the Schick test after this treatment, no further cases developed in the asylum.

The test is now being made on all the students in Western Reserve University Medical School, to establish the mode of procedure in case of an epidemic.